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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/057,467 | 01/22/2002 | Garry P. Nolan | A-64259-2/RMS/AMS | 9737 |

24353 7590 03/21/2006

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| EXAMINER | |
|---|---|
| SMITH, CAROLYN L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1631 | |

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/057,467 | NOLAN, GARRY P. | |
| | Examiner | Art Unit | |
| | Carolyn L. Smith | 1631 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *8-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's remarks, filed 1/19/06, are acknowledged.

Applicant's arguments, filed 1/19/06, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 8-25 are herein under examination.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 8-19, 21, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. (US 5,763,192) in view of Rayner et al. (1994) in view of Gonda et al. (1989) and Scott et al. (1994).

The claims are drawn to a method of screening for phenotypes in cells comprising a library of retroviral vectors comprising random sequences of up to 10 amino acids in length that express peptides comprising an amino-terminal glycine. In some embodiments the random sequences are sequenced after selection and isolation, the cells are mammalian cells, the library comprises up to $10^9$ members, and the inserts are linked to a fusion partner. In some embodiments the phenotype is cell growth or cell death.

Kauffman et al. shows in the abstract and throughout the use of libraries of expression vectors encoding random polypeptides to screen for desired phenotypes. Kauffman et al. shows in column 1 that their method may be used to select for a wide range of properties conferred by the random peptide. Kauffman et al. shows in column 2, lines 13-16 that the expression vector can be viral and the host cell can be a eukaryotic cell. Kauffman shows in column 3, lines 45-56 that beta galactosidase fusion proteins linked to the random sequence have advantages in allowing for purification of the protein. Kauffman et al. shows in column 8, lines 20-22 that the library can have up to a billion members. Kauffman et al. shows in column 12-13 selection of phenotypic properties that affect the survival of the host cell, and selection of polypeptides that catalyze a desired reaction or regulate gene expression in vivo. Kaufman et al. describe selecting proteins that catalyze the synthesis of a specific small peptide, such as a pentapeptide, and that any peptide can be formed in a single step by the terminal condensation of two smaller peptides (col. 14, line 61 to col. 15, line 2). Kauffman et al. does not show use of retroviral vectors, use

of a glycine N-terminal to the randomized insert of up to 10 amino acids in length, use of mammalian host cells, a method of using presentation structures in random peptide libraries, or sequencing the selected inserts.

Rayner et al. shows retroviral vector cDNA libraries in the abstract and throughout. Rayner et al. shows on page 880 that retroviral vectors have advantages of efficiency and stable integration and expression, and allow for selection of phenotypes of infected cells. Rayner et al. show a cDNA library in their retroviral vector with $1.5 \times 10^6$ members on page 882. Rayner et al. shows screening infected mammalian T cells for acquisition of the phenotype of granulocyte-macrophage colony-stimulating factor (GM-CSF) independence in table 2. The sequence of isolated cells with the desired phenotype was determined as shown on page 885, and resulted in confirmation that IL-3 or GM-CSF expressing retroviral library members were in the selected cells. Rayner et al. concludes on page 886 that their method has general utility for isolation of any cDNA for which a functional screen can be devised, including differentiation along pathways that are not normally shown by a particular cell type.

Gonda et al. shows in the abstract and throughout that the amino terminal amino acid of a polypeptide controls the stability of the polypeptide in mammalian reticulocytes. Gonda et al. shows that glycine is among the set of amino acids that confer the highest stability to polypeptides.

Scott et al. describe using random peptide libraries up to 10 amino acids in length (title; page 41, col. 2, last paragraph; Table 1; page 44, col. 2, second full paragraph). Scott et al. reviews random peptide libraries. Scott et al. shows the use of presentation structures to facilitate activity of the random peptide insert on page 40.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Kauffman et al. by use of mammalian cells and retroviral vectors where the motivation would have been to screen libraries in mammalian cells using retroviral vectors because they are efficient and stably integrated, as taught by Rayner et al. (title). It would have been further obvious to sequence the selected clones to further characterize the insert where the motivation would have been to use sequencing to characterize selected inserts, as taught by Rayner et al. (page 885, col. 2, first paragraph). It would have been further obvious to construct the libraries in the method of Kauffman et al. and Rayner et al. of random peptides to contain an amino-terminal glycine residue as taught by Gonda et al. where the motivation would have been to confer stability to polypeptides in mammalian cells, as taught by Gonda et al. (abstract). It would have been further obvious to construct libraries in the method of Kauffman et al., Rayner et al., and Gonda et al. of random peptides of up to 10 amino acids in length as taught by Scott et al. where the motivation would have been to emphasize new approaches for such techniques in order to find ligands that serve as leads for pharmaceutical development purposes (Scott et al., abstract). It would have been further obvious to modify the vectors of Kauffman et al. in view of Rayner et al. in view of Gonda et al. by use of a presentation structure, as taught by Scott et al., where the motivation would have been to help enhance the activity of random peptide inserts, as taught by Scott et al. (page 40).

This rejection is maintained.

Applicants argue that the key to the rejection is the replacement of the "long" random polypeptides in Kaufman et al.'s methods with Scott et al.'s "short" random peptides.

Applicants summarize part of the 103(a) rejection regarding Scott et al. emphasizes new approaches for such techniques in order to find ligands that serve as leads for pharmaceutical development purposes (page 5 of last Office Action). Applicants argue that this falls well short of pointing to any suggestion to express short random peptides in cells in the manner described in Kaufmann. This statement is found unpersuasive for various reasons. It is noted that Kaufman et al. describe selecting proteins that catalyze the synthesis of a specific small peptide, such as a pentapeptide, and that any peptide can be formed in a single step by the terminal condensation of two smaller peptides (col. 14, line 61 to col. 15, line 2). It is noted that the Scott et al. reference was further motivated to combine with the other references because it would have been obvious to modify the vectors in the methods of Kauffman et al., Rayner et al., and Gonda et al. by use of a presentation structure because Scott et al. show that the presentation structures help enhance the activity of random inserts. Applicants wonder what "new approaches" and "techniques" are being referred to in Scott et al. It is noted that Scott et al. are referring to developing epitope library technology. Applicants argue that Scott et al. is completely void of any description of a method that includes phenotypic screening of cells. This statement is found unpersuasive as Kauffman et al., not Scott et al., was relied on for this limitation in the 35 USC 103(a) rejection. It is noted that all limitations of a claim need not come from a single reference in a 35 USC 103(a) rejection. Applicants' arguments are deemed unpersuasive for the reasons given above.

Claim 8, 19, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. in view of Rayner et al. in view of Gonda et al. and Scott et al. as applied to claims 8-10, 11-19, 21, and 22 above, and further in view of Garcia-Bustos et al.

The claims are drawn to a method of using a library comprising nuclear localization signal peptides fused to random peptides.

Kauffman et al. in view of Rayner et al., Gonda et al. and Scott et al., as applied to claims 8-10, 11-19, 21, and 22 above do not describe a method of using a library comprising nuclear localization signal peptides fused to random peptides.

Garcia-Bustos et al. reviews nuclear localization signals. Garcia-Bustos et al. shows on pages 84-85 that fusion of a nuclear localization signal to a protein directs the protein to localize to the cellular nucleus.

Garcia-Bustos et al. state the full potential of a genetic approach in the study of nuclear import has not yet been realized (page 87, col. 1, second paragraph). Garcia-Bustos et al. state proteins are targeted to the nucleus by specific signals (NLSs) that can render a cytoplasmic protein nuclear or when deleted or mutated, no longer promote nuclear uptake of the protein in which they reside (page 88, col. 1, second full paragraph). Garcia-Bustos et al. state nuclear protein localization is subject to complicated regulatory mechanisms since the presence of certain proteins in the nucleus is required only at very specific moments in the cell cycle or only in response to short-lived stimuli (page 98, col. 1, third paragraph). Kauffman shows in column 3, lines 45-56 that beta galactosidase fusion proteins linked to the random sequence have advantages in allowing for purification of the protein. Kauffman describes proteins bound to regulatory proteins controlling transcription activity of nucleic acids (col. 4, lines 32-37).

Rayner et al. mention expression cloning techniques to isolate regulatory molecules involved in regulatory pathways (abstract and page 880, col. 1, first paragraph and col. 2, first full paragraph). It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the proteins in the method of Kauffman et al. in view of Rayner et al., Gonda et al., and Scott et al. by addition of a nuclear localization signal, such as taught by Rayner et al., where the motivation would have been to screen libraries involving regulatory proteins in a practical, efficient, and stably integrated manner and wherein Rayner et al. teaches that retroviral vectors are advantageous for such purposes (abstract). It would have been obvious to include the nuclear protein localization in regulatory pathways of Garcia-Bustos et al. in the method of Kauffman et al. in view of Rayner et al., Gonda et al., and Scott et al. where the motivation would have been to identify defective mutants involving nuclear protein localization in regulatory pathways, as stated by Garcia-Bustos et al. (page 83, first paragraph and page 87, col. 1, second paragraph and page 99, col. 1, second paragraph).

This rejection is maintained.

Applicants argue that the rejection is deficient for providing inadequate motivation to combine references for the same reasons set forth above, and that Garcia-Bustos' reference fails to remedy the key deficiency outlined above. This statement is found unpersuasive as Applicants' arguments were deemed unpersuasive above, and motivations to combine the various references are specifically set forth above.

Claims 23-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauffman et al. in view of Rayner et al., Gonda et al., and Scott et al. as applied to claims 8-10, 11-19, 21, and 22 above, and further in view of Abbas et al.

The claims are drawn to a method of using a library of random peptides to modulate cellular differentiation. In some embodiments the differentiation markers are characteristic of T-cells or B-cells.

Kauffman et al. in view of Rayner et al., Gonda et al., and Scott et al., as applied to claims 8-10, 11-19, 21, and 22 above does not show alterations of differentiation markers that are characteristic of T cell or B cell activation.

Abbas et al. reviews T cell and B cell differentiation particularly on pages 236-239.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to extend the screening of phenotypes of Kauffman et al. in view of Rayner et al. in view of Gonda et al. and Scott et al. to determine states of differentiation of T cells and B cells as taught by Abbas et al. where the motivation would have been to allow researchers to gain further insights into the mechanisms of regulation of differentiation of T cells and B cells by such screening and where Abbas et al. state that such differentiation is important in the function of the immune system.

This rejection is maintained.

Applicants argue that the rejection is deficient for providing inadequate motivation to combine references for the same reasons set forth above, and that Abbas' reference fails to remedy the key deficiency outlined above. This statement is found unpersuasive as Applicants' arguments were deemed unpersuasive above, and the motivation is set forth above.

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

MARJORIE A. MORAN
PRIMARY EXAMINER

Marjorie A. Moran
3/15/06

March 14, 2006